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Extracellular S100A4 induces arterial smooth muscle cell activation in a RAGE-dependent manner

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Background: It has been proposed that smooth muscle cells (SMCs) from the arterial wall are heterogeneous and that only a subset of medial SMCs are prone to accumulate into the intima leading to atheromatous plaque formation. We isolated 2 distinct SMC phenotypes from porcine coronary artery: spindle-shaped (S) and rhomboid (R). Biological features of R-SMCs (i.e. enhanced proliferative and migratory activities as well as poor level of differentiation) explain their capacity to accumulate into the intima. We identified S100A4 as being a marker of the R-SMCs in vitro and of intimal SMCs, both in pig and human. S100A4 is a Ca2+-binding protein that can also be secreted; it has extracellular functions probably via the receptor for advanced glycation end products (RAGE).

Purpose: Explore the role of S100A4 in SMC phenotypic change, a phenomenon characteristic of atherosclerotic plaque formation.

Methods and Results: Transfection of a human S100A4-containing plasmid in spindle-shaped (S) SMCs (devoid of S100A4) led to approximately 10% of S100A4-overexpressing SMCs, S100A4 release, and a transition towards a R-phenotype of the whole SMC population. Furthermore treatment of S-SMCs with S100A4-rich conditioned medium collected from S100A4-transfected S-SMCs induced a transition towards a phenotype typical of the R-SMCs, which was associated with decreased SMC differentiation markers, increased proliferation and migration, as well as induced proteolytic activity through activation of urokinase-type plasminogen activator (uPA), matrix metalloproteinases (MMP-1,-2, -3, and -9) and their inhibitors (TIMP-1). Furthermore, extracellular S100A4 yielded activation of NF-kB in a RAGE-dependent manner. Blockade of extracellular S100A4 in R-SMCs with S100A4 neutralizing antibody induced a transition from R- to S-phenotype, decreased proliferative activity and upregulation of SMC differentiation markers. In contrast, silencing of S100A4 mRNA in R-SMCs did not change the level of extracellular S100A4 nor SMC morphology in spite of decreased proliferative activity.

Conclusions: Our results indicate that SMC phenotypic changes are essentially dependent on extracellular S100A4 activity. It could be a new target to prevent SMC accumulation during atherosclerosis and restenosis.